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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/568,628	09/05/2006	Hirohiko Hohjoh	U 016154-7	2748

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EXAMINER	
CHONG, KIMBERLY	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/568,628	HOHJOH, HIROHIKO	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *24,25,27 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23,26,29 and 30* is/are rejected.

7)☒ Claim(s) *6-8, 10, 19-21, 23* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 September 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/15/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-23, 26 and 29-30 in the reply filed on 11/05/2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The requirement is still deemed proper and is therefore made FINAL.

Status of the Application

Claims 1-30 are pending. Claims 1-23, 26 and 29-30 are currently under examination. Claims 24-25 and 27-28 are withdrawn as being drawn to a non-elected invention.

Drawings

The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the description: Specifically, Figure 2 recites two graphs identified as "2a" and "2b" however reference to part 2a is not mentioned in the brief description nor in the detailed description of the invention. Corrected drawing sheets in compliance with 37 CFR 1.121(d), or amendment to the specification to add the reference character(s) in the description in compliance with 37 CFR 1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing

on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

The spacing of the lines of the specification is such as to make reading difficult. New application papers with lines 1½ or double spaced on good quality paper are required.

Information Disclosure Statement

The information disclosure statement filed 02/15/2006 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because The non-patent literature document listed as AR does not include the author of the reference. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Claim Objections

Claims 6-8 and 19-21 are objected to because of the following informalities: The claims are grammatically incorrect because they are missing the article "the" in the sentence. Claims 6 and 19 recite "...located at nucleotide position 1-3 in 5'- or 3'- direction" and correction of sentence to recite "...located at nucleotide position 1-3 in *the* 5'- or 3'- direction..." would obviate the rejection of claims 6 and 19. Claims 7 and 20 recite "...located at nucleotide position 1-3 in 5'-direction..." and correction of the sentence to recite "...located at nucleotide position 1-3 in *the* 5'-direction..." would obviate the rejection of claims 7 and 20. Claims 8 and 21 recite "...located at nucleotide position 2 in 5'-direction..." and correction of the sentence to recite "...located at nucleotide position 2 in *the* 5'-direction..." would obviate the rejection of claims 8 and 21.

Claims 10 and 23 are objected to because of the following informalities: Claims 10 and 23 recite the double stranded RNA molecule "which has a strand length of 29 or less nucleotides". The dsRNA has two strands and therefore amending the claim to recite "wherein each strand has a strand length of 29 or less nucleotides", for example, would obviate this rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5, 9-18, 22-23, 26 and 29-30 are rejected under 35 U.S.C. 102(e) as being anticipated by Zamore et al. (US 2005/0186586) as evidenced by Aravin et al. (Developmental Cell, 2003) and Elbashir et al. (Nature 2001).

The claims are drawn to a double stranded RNA (dsRNA) molecule capable of suppressing the expression of a target gene in a cell by RNAi wherein one or more nucleotides in order from the 3' end of the sense strand or one or more nucleotides in order from the 5' end of the sense strand of the double stranded part of the molecule are not complementary to the antisense strand, wherein the number of nucleotides that are not complementary are 1 to 4 or 2, wherein on additional nucleotide located at position 11-13 or position 12 from the 3' end of the sense strand is not complementary to the antisense strand, wherein one additional nucleotide located an position 1-3 in the 5' or 3' direction from a site on the sense strand of the double stranded part is not complementary to the antisense strand, wherein the dsRNA does not induce double stranded protein kinase in a cell, wherein the dsRNA has a strand length of 29 nucleotides or less and drawn to dsRNA wherein either the 5' end of the antisense or the 5' end of the sense strand are guided into the RISC.

Regarding instant claims 1-3, Zamore et al. teach a dsRNA comprising a sense and antisense strand wherein up to 4 nucleotides on the sense strand are not complementary to the antisense strand (see Figure 21E). Zamore et al. refers to the antisense strand as being the guide strand that is complementary to the target sequence and is capable of being loaded into the RISC complex (see paragraph 0088). In Figure 21E, the antisense strands are SEQ ID Nos. 127, 128, 130 and 131.

Regarding claims 4-5, Zamore et al. teach a dsRNA molecule having one or more nucleotides from the 3' position of the sense strand not complementary to the antisense strand and having a mismatch at position 12 from the 3' end of the sense strand (see Figure 6A, specifically mir-6-3). The dsRNA sequences listed in Figure 6A are duplexes wherein the sequence shown as italicized is a known miRNA sequence and as evidenced by Aravin et al., this miRNA sequence is a guide sequence, i.e. antisense strand, that is involved in guiding the RNA degradation of a target sequence (see pages 341-342 and last paragraph). Therefore, the italicized sequence of the dsRNA in Figure 6A is the sequence that is complementary to the target sequence and is therefore considered the antisense sequence in the dsRNA (as defined in the instant specification in paragraph 0017). It must be noted that claim 1 is not limited to just the non-complementary nucleotides being located at the 3' end of the sense strand. Claim 1 recites the dsRNA "is designed such that one or more nucleotides in order from the 3' end of the sense strand ...are not complementary" and this limitation does not preclude any other nucleotide from

not being complementary to the antisense strand as long as there is an adequate number of nucleotides to enable hybridization of both strands.

Regarding instant claims 9-10 and 22-23, Zamore et al. teach the dsRNA are capable of eliciting RNAi in mammalian cells and are preferably between 16-25 or 18-23 nucleotide base pairs in length which as evidenced by Elbashir et al. do not induce double-stranded RNA-dependent protein kinase. Elbashir et al. specifically teach dsRNA 30 nucleotides or less do not induce said kinase activity in cells (see pages 494-495).

Regarding instant claims 11-13, Zamore et al. teach a dsRNA wherein 1 to 4 nucleotides starting from the 5' end of the sense strand of the double stranded part of the molecule is not complementary to the antisense strand (see Figure 14A). Regarding claims 14-16, Zamore et al. teach a dsRNA wherein one or more nucleotides starting from the 5' end of the sense strand of the double stranded part of the molecule is not complementary to the antisense strand and wherein one or more additional nucleotides, or 1 to 4, or 2 nucleotides in order from the 3' end of the sense strand of the double-stranded part are not complementary to the antisense strand (see Figure 21E). Regarding claims 17-18, Zamore et al. teach a dsRNA wherein one nucleotide at the 5' end of the sense strand of the double stranded part of the molecule is not complementary to the antisense strand and wherein position 12 from the 3' end of the sense strand is not complementary to the antisense strand (see Figure 6A, sequence miR-7). It must be noted that claim 11 is not limited to just the non-complementary nucleotides being located at the 5' end of the sense strand. Claim 11 recites the

dsRNA "is designed such that one or more nucleotides in order from the 5' end of the sense strand ...are not complementary" and this limitation does not preclude any other nucleotide from not being complementary to the antisense strand as long as there is an adequate number of nucleotides to enable hybridization of both strands. Therefore, the sequence miR-7 meets the limitations of the claim even though it has additional nucleotides on the sense strand that are not complementary to the antisense strand.

Regarding claim 26, Zamore et al. further teach vectors capable of expressing said dsRNA in cells (see paragraphs 0150-0153). Regarding claims 29-30, Zamore et al. teach dsRNA wherein the 5' end of the antisense strand is incorporated into the RISC more efficiently and teach a dsRNA wherein the 5' end of the sense strand is incorporated into the RISC compared to the other strand (see Figure 3, particularly Figures 3C and 3H and paragraphs 0274-0277). Zamore et al. teach dsRNA with either end comprising non-complementary nucleotides determines which sequence is guided into the RISC (see paragraph 0277).

Thus Zamore et al. anticipates claims 1-5, 9-18, 22-23, 26 and 29-30 of the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-23, 26, 29 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zamore et al. (US 2005/0186586) as applied to claims 1-5, 9-18, 22-23, 26 and 29-30 above, and further in view of Abdelgany et al. (Human Molecular Genetics, 2003, Vol. 12, No. 20: 2637-2644).

Claims 1-5, 9-18, 22-23, 26 and 29-30 are drawn to the invention as stated above. Claims 6-9 and 19-21 are further drawn to a dsRNA wherein one or more mismatches from the 3' end of the sense strand of the double stranded region of the molecule are not complementary to the antisense strand and further wherein one additional nucleotide located at position 1-3 or 2 from the 3' or 5' direction from the nucleotide in the center of the sense strand is not complementary to the antisense strand wherein the site is corresponding to the cleavage site of the target gene transcription product by RISC.

Zamore et al. is relied upon as above. Zamore et al. additionally teach a dsRNA with 4 nucleotide mismatches in the central region of the duplex bound more tightly to the RISC complex (see paragraph 0309) and thereby was capable of guiding RNA interference of the target gene. Zamore et al. does not specifically teach the mismatches in positions 1-3 or 2 in the 3' or 5' direction from a site in the center of the sense strand and does not teach the site corresponds to the cleavage site of the target gene transcription product by RISC.

Abdelgany et al. teach optimizing a siRNA molecules ability to silence gene expression by designed dsRNA comprising nucleotide mismatches at several positions in the duplex at or near the target cleavage site (see 2639). Abdelgany et al. found that certain mismatches in the center of duplex region either resulted in a greater or lesser degree of transcript silencing and showed said mismatches, in this case position 10, allowed discrimination between the mutant and wild-type allele AChR mutant gene.

It would have been obvious to one of skill in the art to place mismatched nucleotide sequences in the central region of a dsRNA around the target cleavage site, as taught by Abdelgany et al. and Zamore et al.

One would have been motivated and it would have been a matter of routine optimization to design the dsRNA, taught by Zamore et al., wherein the dsRNA has additional mismatched nucleotides near the target cleavage site because Abdelgany et al. teach such mismatches aid in the discrimination of mutant alleles targeted by the dsRNA and leads to silencing of mutant gene expression while allowing for expression from the wild-type gene. Given that Zamore et al. teach centrally located mismatches allow for better binding of the strand to the RISC, one would have been motivated to find the optimal position for placement of the mismatch to target mutant alleles given the fact that mismatches have been demonstrated to be tolerated by the duplex and still capable of loading into the RISC and mediating gene silencing.

One would have expected to be able to incorporate mismatches at or near the cleavage site and would have been expected to be able to find the optimal

position of mismatches in the central region of the duplex given Abdelgany et al. teach methods of positioning the mismatches in a duplex that still allow for the siRNA to mediate gene silencing.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the

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/Kimberly Chong/
Examiner
Art Unit 1635